REMARKS

Claims 1-4, 7-12, 14, 18-22, and 24-26. By the present communication, claims 1-4, 11, 12, 18-22, 25, and 26 have been amended. These amendments add no new matter as the claim language is fully supported by the specification and original claims. The subject amendments present the claims in condition for allowance or, at a minimum, in better form for appeal. Accordingly, entry of this amendment is respectfully requested. Subsequent to the entry of the present amendment, claims 1-4, 7-12, 14, 18-22, and 24-26 are pending and at issue.

I. Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 1-4, 7-12, 14, 18-22, and 24-26 are rejected under on 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

As a preliminary matter, Applicants respectfully remind the Examiner that the present claims are based on the unexpected finding that,

> nucleic acid having a mutant nucleotide sequence associated with a primary tumor is detectable in the adjacent histopathologic surgical margins and more distant tissues, such as regional lymph nodes, which are apparently "normal" when examined by standard histological techniques.

Specification at page 4, lines 2-6. Moreover,

> As a consequence of this discovery, the present invention represents a significant advance over such standard medical techniques as visual, light microscopy tissue biopsy and morphologic assessment of such tissue, by providing a rapid, and accurate molecular biologic method for detecting at the molecular level mutant nucleotide sequences associated with a primary tumor. The approach of the invention is based upon DNA amplification and can identify as few as a single cell carrying a mutant gene among a large excess (greater than 10,000) of normal cells.

Specification at page 4, lines 8-15. Based on this discovery, the present claims are directed to methods of detecting defined target neoplastic nucleic acids having mutant nucleotide sequences, which are present in a primary neoplasm, in histologically normal tissue specimens. Such methods provide the advantage of detecting the metastasis of a small number of tumor cells into normal tissue *before* such cells are able to grow into a tumor that is visible by standard histologic methods.

According to the Office Action "the claims lack enablement because it has not been established that nucleic acids meeting the requirements of the claims may actually be detected in specimens at a point in time when those specimens still appear 'histologically normal'" (Office Action, page 4). It is respectfully submitted that the claims are fully enabled by the present disclosure and that which was known in the art at the time of filing of the present application.

The present claims are directed to method of detecting a mutant nucleotide sequence of a neoplastic nucleic acid (e.g., APC, DCC, NF1, NF2, RET, VHL, or WT-1) in nucleic acids extracted from a tissue specimen external to the neoplasm. For example, the present invention as described by claim 1 the detection of a mutant nucleotide sequence that "is present in the primary neoplasm," in nucleic acid extracted from a tissue specimen, which is "external to the neoplasm" and is "histologically normal." The specification provides abundant guidance for the practice of the claimed methods as well as a detailed working example. Specifically, Applicants disclose that mutant p53 nucleic acid present in metastatic tumor cells can be detected in tissues (e.g., tumor surgical margin and lymph nodes) containing a small number of such metastatic tumor cells, even though such tissues appear histologically normal. This example provides the general teaching that tumor cells that metastasize from a primary tumor can be identified in otherwise normal-appearing tissues by detecting the mutant target nucleic acid in such normal-appearing tissue. Thus, based on this disclosure, one of skill in the art would have reasonably expected that mutations in any of the other recited tumor suppressor genes, which are found in the primary tumor, could similarly be detected in histologically normal tissue containing metastatic tumor cells from the primary tumor.

Therefore, in order to practice the claimed method, the skilled artisan simply need know whether one or more of the target neoplastic nucleic acids is present in a mutated form in the primary neoplasm. As stated in the specification at for example Table 1, and as is known in the art, tumor suppressor genes (e.g., APC, DCC, NF1, NF2, RET, VHL, and WT-1) and mutated forms thereof have been associated with specific cancer types. Armed with this knowledge, the skilled artisan can readily assay the neoplasm and a histologically normal tissue specimen for the mutant nucleotide sequence of the relevant tumor suppressor gene using the methods exemplified for p53.

The Examiner further asserts that the prior art as exemplified by Nees *et al.* (*Cancer Research* 53:4189-96, 1993) "indicates that it is unknown what genes other than p53 might be detectable in specimens that appear normal by histological analysis" (Office Action at page 4). It is respectfully submitted that the teaching of Nees *et al.* is not relevant to the claimed methods. Nees *et al.* is concerned with the genetic changes underlying the development and progression of head and neck cancer, in particular, "the occurrence of multiple primary, secondary, and recurrent tumors (also referred to as field cancerization)" (Nees *et al.* at page 4194, column 1) and suggests a multifocal polyclonal process to explain this phenomenon, substantiated by the identification of <u>different</u> p53 mutations in primary and secondary tumors (Nees *et al.* at page 4195, column 2). In contrast, the present claims provide a means to detect neoplastic cells that have migrated (e.g., by invasion or metastasis) from the primary neoplasm into histologically normal tissue by detecting the presence of the <u>same</u> mutation that is present in the primary tumor.

In summary, it is submitted that one skilled in the art, in view of the present specification and that which was known in the art, would reasonably have predicted that the disclosed methods could be applied to the detection of a mutant form of any of the recited tumor suppressor genes, wherein that same mutation is present in the primary tumor, in histologically normal tissues harboring a small number of metastasized tumor cells from the primary tumor. Accordingly, the

skilled artisan would have known how to practice the claimed methods without undue experimentation.

Accordingly, withdrawal of rejection of claims 1-4, 7-12, 14, 18-22, and 24-26 under 35 U.S.C. §112, first paragraph is respectfully requested.

II. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1-4, 7-12, 14, 18-22, and 24 stand rejected under 35 U.S.C. §112, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

The Examiner asserts that the phrase "extracting the nucleic acid present in the neoplasm, wherein the nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1" in claim 1 is allegedly indefinite because it is unclear whether the extraction is of any nucleic acid or only the target molecule. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, this claim has been amended herein to further clarify that the extracting refers to "the nucleic acid present in the neoplasm and in the histologically normal tissue specimen." Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that the phrase "detecting the nucleic acid in the neoplasm and in histologically normal tissue specimen" in claim 1 is allegedly indefinite because it is unclear whether "the nucleic acid" refers to the recited nucleic acid present in the neoplasm or to a particular target molecule. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, this claim has been amended herein to further clarify that the "detecting" refers to the target molecule. Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that it is allegedly unclear how the "histologically normal tissue specimen" relates to the "tumor margin tissue specimen" in claim 1. Without acquiescing

to the reasoning offered by the Examiner and to expedite prosecution, claim 1 has been amended to delete the phrase "histologically normal tissue specimen." Thus, as currently amended, claim 1 recites a tumor margin tissue specimen that is "histologically normal." Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that the claim 1 recites an objective of detecting a "mammalian mutant target nucleic acid in a neoplasm and in a tumor margin tissue specimen" but allegedly does not indicate how the objective is achieved. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, this claim has been amended herein to reflect that the "mutant nucleotide sequence" of the preamble, is detected in the final step of the claim. Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that claims 2, 3, and 11 are allegedly indefinite because claim 2, depending from claim 1, recites a step of "detecting the presence of the mutant target nucleic acid" which is not present in claim 1. As presently amended, claim 2 recites the step of "detecting the mutant nucleotide sequence," which is the final step of claim 1. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner further asserts that the phrase "selected from at least APC, DCC, NF1, RET, VHL, and WT-1" in claim 12 is allegedly indefinite because the term "at least" suggests that one could choose a gene other than those listed. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, this claim has been amended herein to delete the term "at least." Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that the phrase "the target mutant neoplastic nucleic acid" of claim 18 is allegedly indefinite because there is insufficient antecedent basis for this phrase. As presently amended, the claim recites a final step of "detecting the presence of the mutant nucleotide sequence in the extracted nucleic acid and in the tissue specimen, wherein the target neoplastic nucleic acid is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1." Thus,

the phrase "target mutant neoplastic nucleic acid" has been replaced with "mutant nucleotide sequence" or "target neoplastic nucleic acid," both of which find antecedent basis in the preamble of the claim. Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that the phrase "isolating a tissue specimen wherein the tissue specimen appears histologically normal" of claim 19 is allegedly indefinite because it is unclear how this step relates to the other steps of the claim. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, the "isolating" step precedes the "extracting" step. Withdrawal of this rejection is respectfully requested.

The Examiner further asserts that the phrase "the target mutant neoplastic nucleic acid" of claim 19 is allegedly indefinite because there is insufficient antecedent basis for this phrase. As presently amended, this phrase has been replaced with "target neoplastic nucleic acid," which finds antecedent basis in the preamble of the claim. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner further asserts that claims 20-22 and 24 are allegedly indefinite because claim 20 appears to contain multiple tissue specimens, thus it is unclear which specimen is the "tissue specimen" recited in the detecting step. The Examiner also asserts that the it is allegedly unclear how the "isolating" step relates to the prior step of extracting nucleic acid. Without acquiescing to the reasoning offered by the Examiner and to expedite prosecution, the claim recites an "isolating a lymph node tissue specimen" step that precedes the "extracting" step. Withdrawal of this rejection is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants ' undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge $1810.00 as payment for the Petition for Three-Month Extension of Time fee ($1020.00) and Request for Continued Examination fee ($790.00) to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213